REMARKS

Reconsideration of the above-identified application in view of the amendments above and the remarks following is respectfully requested. Claims 1-39 are in this case. Claims 1-39 have been rejected. Claims 1-39 have now been canceled without prejudice. New claims 40-90 have been added.

The Applicant respectfully wishes to point out that the present Office Action was apparently issued with regard to the claims of the original PCT application PCT/IL00/00364 as filed, comprising 39 claims, and not with regard to the amended claims as transmitted by the International Bureau under PCT Article 19 (35 U.S.C. 371(c)(3)), which included 49 claims.

For the purposes of clarification only and without any intention to alter the scope of the claims (except where noted below), claims 1-39 have been canceled without prejudice and replaced with a substitute set of claims 40-46 and 49-89, corresponding to claims 1-49 of the previously amended Application. New claims 47, 48 and 90 have been added as described below.

OBJECTED CLAIMS

The Examiner has rejected original claims 1 and 7 under 35 U.S.C. 112, second paragraph, as being indefinite. While continuing to traverse the rejections of the Examiner, Applicant has chosen to expedite the prosecution by amending claim 46, corresponding to original claim 7, to delete the reference to hydroxypropyl methylcellulose (HPMC).

Rejections over 35 USC 102

The Examiner has rejected claims 1-3, 5, 7-10, 14, 15, 17-19, 21-25, 29, 30, 32, 33, 36, and 37 under 35 U.S.C. 102(b) as being anticipated by Dietrich et al. (WIPO Publication No. WO 99/27917). The rejections of the Examiner are respectfully traversed.

Dietrich teaches a preparation in the form of a pellet or tablet for acid-labile active substances, comprising an alkaline core and a gastric juice-resistant coating comprising a neutralized film former

The publication date of this WIPO publication is June 10, 1999. This is only 12 days before the claimed priority date of June 22, 1999 for the present Application. As supported in the attached affidavit, Applicant declares that conception of Applicant's invention occurred

sometime before June 10, 1999, and that diligence was observed during the period between conception of the invention and publication.

The present invention relates to a novel stable formulation for an acid labile benzimidazole, and methods of preparation and administration thereof, and in particular to a stable formulation of a benzimidazole, which is suitable for oral administration. The formulation is able to maintain the stability of a benzimidazole derivative, such as Omeprazole during storage and during the passage through the stomach without a separating layer. The single layer enteric coating is applied as a solution with a pH value of at least 6.5 directly to the benzimidazole substrate, without the use of a subcoat, or any intermediate layer, and remains basic during storage and administration. Conversion of the enteric coating to an acidic form may occur only after the preparation reaches the stomach.

Dietrich teaches a partially neutralized film former (page 6, lines 17-20). In a preferred embodiment of the formulation, the film former which is applied to the core is treated with a base to neutralize the free carboxyl groups of the film former (page 10, lines 17-20), while a dispersion of non-neutralized stomach acid resistant film former or any desired stomach acid resistant coating is also applied until a sufficient thickness is achieved (page 11, lines 11-14).

The neutralized film former usually has a pH value of 4 to 8, i.e. in the neutral range (page 11, lines 3-6). Higher pH values are mentioned as being 'not disadvantageous' (page 11, lines 6-8), therefore a coating layer having a high pH is clearly not the taught invention.

Dietrich describes (page 11, lines 10-17) separate application of a film polymer having neutralized carboxyl groups, and of a second layer comprising a dispersion of non-neutralized stomach acid resistant polymer film former, which is also sprayed on. Therefore, Dietrich does not teach a homogenous enteric coating layer or a homogenous solution for producing such a homogenous layer.

The use of at least two enteric coating layers is therefore taught, in contrast to the single layer of the present invention.

Furthermore, the taught neutralized film layer has relative basicity with respect to the acidic outer coating layer, which, as is well known in the art (for example, with regard to EP 247983), would be expected to lead to interaction between the two layers resulting in degradation of the acid outer coating layer. In an alternative embodiment of the invention taught by Diedrich, the transition from neutralized to untreated film material is continuous (page 11, lines 17-19). A description of a device for continuous application of coating

material, showing transition from neutralized to non-neutralized material, is described in the paragraph on page 11, line 16 to end, and bridging page 12, lines 1 to 15). The composition of the device is continuously modified from 'neutralized' to 'non-neutralized', such that at the end of the process preferably no neutralized film former is present in the container. The result is therefore a non-neutralized outermost layer over a neutralized sub-layer.

Hence the invention taught by Dietrich teaches a film coating having a pH of preferably neutral value, with a continuous gradation of the pH value of the coating. Application of this graduated layer clearly results in non-homogeneous coating of the tablet, as a portion of the coating material is non-homogeneous while another portion is homogeneous, particularly as compared to the uniform enteric coating of the present application.

In either example, the outer layer taught by Dietrich is non-neutralized, with an acidic pH.

Dietrich does not teach or suggest the use of a uniform enteric coating of pH preferably from 7 to about 10.

Furthermore, in the invention taught by Dietrich, the core comprises the active substance. Dietrich does not teach an embodiment comprising a neutral core with an active layer containing the active substance, as recited in amended claim 44 of the present application.

While continuing to traverse the rejections of the Examiner, Applicant has chosen to amend certain claims and to add new claims as follows, in order to expedite the prosecution.

Original claim 1 (corresponding to new claim 40) has been amended to recite a homogenous layer of enteric coating material being layered over the core. Support for this is found throughout the specification, and specifically at page 8, lines 11-12, which describe the coating solution being applied directly to the substrate without any need for an additional layer. This clearly teaches the use of a single coating layer. The use of a single solution for application as the enteric coating layer is taught throughout the description and associated examples. No mention is made at any point of use of more than one solution and/or of a non-homogenous solution or material as a coating. It is therefore clearly understood that a homogenous solution is used.

Original claim 8 (corresponding to new claim 48) has been rewritten as an independent claim reciting HPMCP in combination with at least one other enteric coating polymer. Support for this amendment may be found throughout the specification, including

at page 12, lines 4 to 6, which states that HPMCP may be used in combination with at least one of the other listed enteric coating materials.

Original claim 31, corresponding to new claim 71 has been amended to delete the reference to hydroxypropylcellulose (HPC), and to replace HPMC with hydroxypropyl methylcellulose (HPMCAS). Support for this is derived from the specification at page 12, line 8, which describes HPMCAS as the preferred enteric coating material.

New claim 47 has been added to recite an active coating comprising hydroxypropyl methylcellulose. Support for this is derived from the specification in Examples 4, 16, 17, 18, and 19 (at pages 18, 35, 37, 38, and 40, respectively.

New claim 90 has been added to recite a single, homogenous layer of enteric coating. Support for this is found throughout the specification, and specifically at page 8, lines 11-12, which describe the coating solution being applied directly to the substrate without any need for an additional layer. This clearly teaches the use of a single coating layer. The use of a single solution for application as the enteric coating layer is taught throughout the description and associated examples. No mention is made at any point of use of more than one solution and/or of a non-homogenous solution or material as a coating. It is therefore clearly understood that a homogenous solution is used.

Rejections over 35 USC 103

The Examiner has rejected claims 1-39 under 35 U.S.C. 103(a) as being unpatentable over Dietrich et al. in view of Lundberg et al. (U.S. Patent No. 6,013,281) and Lee et al. (U.S. Patent No. 6,228,400 B1). The rejections of the Examiner are respectfully traversed.

The object of Dietrich is described above.

Lundberg teaches an oral pharmaceutical dosage form comprising an alkaline reacting core material and an enteric coating layer, such that a separating layer is formed in situ as a water soluble salt between the alkaline core material and the enteric coating polymer.

The object of the present invention is a formulation which is characterized by the lack of a separating layer between the core and the enteric coating layer. No reaction such as that described by Lundberg occurs between the enteric coating and the core material in the formulation of the present invention, since a neutralized enteric coating layer is used, having a pH value of at least 6.5. As stated on page 6, lines 7-10, interaction between the enteric coat and the alkaline core is completely eliminated as the enteric coat is not acidic. The

enteric coating polymer is neutralized before the coating process, and sprayed directly onto the core. The use of a neutralized enteric coating polymer which overcomes the need for a separating layer, either pre-formed or formed in situ, is neither taught nor suggested by Lundberg.

Lundberg also teaches away from the present invention, such that Lundberg would not lead one of ordinary skill in the art to attempt to combine Lundberg with Dietrich.

The patent application which matured into Lee, filed January 19, 2000, has a priority date later than that of the June 22, 1999 priority date of the present Application, for which priority was derived from Israeli prior application no. 130602. The Official USPTO Filing Receipt of March 11, 2003, incorrectly failed to cite the parent Israeli application. A copy of the request for correction of the filing receipt is attached. Hence, the document to Lee cannot be considered as prior art in respect of the present Application.

Furthermore, US 6,228,400 to Lee teaches a formulation comprising a subcoat that is required between the core and the enteric coating. A formulation in which no subcoat is present, while a neutralized enteric coating is present, is not taught. Lee also teaches away from the present invention, such that Lee would not lead one of ordinary skill in the art to attempt to combine Lee with Dietrich.

Therefore, the combination of Dietrich and Lundberg clearly does not teach the present invention, nor does the combination of Dietrich, Lundberg and Lee.

The present response is intended to be fully responsive to all points of objection raised by the Examiner and is believed to place claims 40-90 in condition for allowance. Favorable reconsideration and allowance of the Application is respectfully requested.

Respectfully submitted,

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